COMPOSITION PULSE TIME-OF-FLIGHT

MASS FLOW SENSOR

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001]   This application is a Continuation-in-Part of prior co-pending application serial no. 10/210,647, filed 07/31/2002, now abandoned.

STATEMENT OF GOVERNMENT INTEREST

[0002]   This invention was made with Government support under contract no. DE - AC04 - 94AL85000 awarded by the U. S. Department of Energy to Sandia Corporation. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003]   The present invention relates generally to a device, capable of operating at high pressure, for the detection of fluid flow rates over a wide range of flow rates (<1 nL/min to >10 μL/min) and particularly for measuring fluid flow rates in microfluidic devices.

BACKGROUND OF THE INVENTION

[0004]   Numerous types of mass flow meters are generally available. Some are based on viscous drag, others employ the Venturi effect to measure a pressure drop, still others use positive displacement either rotary or linear. For low flow rates, local heating of a passing fluid and a variation in the resistance of a resistive element or the current/voltage required to maintain a

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constant temperature/current in the resistive element is
conventionally used to determine fluid flow rate,
wherein the fluid can be either a liquid or a gas.
Rudent et al. in U.S. Patent No. 6,354,150 "Sensor for a
Capillary Tube of a Mass Flow Meter", issued Mar. 12,
2002, describe a mass flow rate sensor based on the
time-of-flight of a thermal pulse. The time-of-flight
of a small volume of liquid is measured from an upstream
position where the temperature is modified to a
downstream detector. However, the thermal sensor
requires specially insulated components to avoid thermal
transients, which can be a disadvantage.

[0005]   Wu and Sansen (Wu, J. and Sansen, W.
Electrochemical time of flight flow sensor, Sensors and
Actuators, 97, 68-74, April 1, 2002) describe a time of
flight flow sensor for measuring the flow rates of
aqueous fluids in the range of 1-15 µL/min. The device
uses an in situ electrochemically produced tracer to
determine fluid flow rate and is comprised of two
electrochemical cells integrated in the flow channel.
An upstream electrochemical cell functions as an oxygen
producer and a downstream electrochemical cell functions
as an amperometric oxygen detector. Oxygen produced at
the upstream cell by an electrochemical pulse is
detected at the downstream amperometric cell and the

flow rate is determined by the time difference between
the two pulses. However, this device suffers from the
limitation that it is unable to measure fluid flow rates
less than about 1 μL/min (1000 nL/min) due to
limitations of the oxygen sensor (*ibid.*, p. 71).

SUMMARY OF THE INVENTION

[0006]   The invention is directed generally to a device and
method for measuring fluid flow rates that can range
from less than 1 nL/min to greater than 10 μL/min, and
particularly for measuring flow rates in microfluidic
devices. The invention operates by producing localized
compositional variations in the fluid at distinct
locations along the flow axis. The time required for
the compositional variation, or pulse, to be detected
downstream from its point of creation is used to derive
a flow rate. The pulse, comprising a narrow zone in the
fluid whose composition is different from the mean
composition of the fluid, can be created by
electrochemical means, such as by electrolysis of a
solvent, electrolysis of a dissolved species, or
electrodialysis of a dissolved ionic species.

[0007]   In contrast to prior art thermal flow sensors, the
present invention is thermally robust in that no
insulation is required to avoid thermal transients and
it retains superior sensitivity as it is scaled down to

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the nanoliter flow rate regime and sub-millimeter
dimension. Decreasing the scale of thermal flow sensors
increases the heat transfer rate from the heated fluid
volume to the surroundings due to a high surface-to-
volume ratio and small length scale. This results in
poor signal-to-noise at small flow rates ($\approx$nL/min). In
contrast, a composition pulse, such as produced here,
retains its signal-to-noise ratio because mass diffusion
is confined to the fluid and mass diffusivity is much
smaller than thermal diffusivity. Moreover, this device
is capable of operating at pressures as great as 2,000
psi, limited only by the strength of the materials of
construction.

[0008]   The invention is directed to a device for detecting
the mass flow rate of a fluid that includes:

        means for producing localized compositional
variations in the fluid along the flow axis; and

        means for subsequently detecting the compositional
variation at a point downstream from its point of
creation, wherein said device is capable of measuring
flow rates from less than about 1 nL/min to greater than
about 10 μL/min at pressures as great as 2,000 psi.

        In one embodiment of the invention, the device
comprises:

        spaced-apart electrodes disposed along the flow

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axis in a fluid flow channel;

means for supplying a voltage to the electrodes to produce a local compositional variation in a fluid;

means for detecting the compositional variation; and

means for determining time-of-flight of the variation.

[0009]   It can be advantageous to incorporate a flight tube into the flow channel as part of the detector means. The flight tube is concentric with flow channel and adjoined to the fluid exit of the flow channel and preferably smaller in diameter than the flow channel in order to achieve a high Reynolds number for rapid transport of the ions to the bulk flow. As will be appreciated by those skilled in the art, the dimensions of the flight tube can be selected for a particular flowrate range, fluid viscosity, and ion diffusivity to govern mass transport and hence, the response time and sensitivity of detection of the pulse produced by the upstream electrodes.

[0010]   Thus, in another embodiment the invention is directed to a device for detecting the mass flow rate of a fluid in a flow channel that can be a capillary channel or microfluidic device that includes:

a flight tube attached to the fluid exit of the

flow channel and concentric with the flow channel, wherein the internal diameter of the flight tube is less than that of the flow channel;

at least a pair of spaced-apart electrodes disposed along the flow axis in a fluid flow channel;

means for supplying a voltage to the electrodes to produce a local compositional variation in a fluid;

means for detecting the compositional variation, wherein said means for detecting is disposed in said flight tube; and

means for determining time-of-flight of the variation.

[0011]   For those applications wherein the fluid flow rate is in the range of less than about 100 nL/min to greater than about 500 nL/min, measurement of the fluid flow rate using the aforementioned configuration can be difficult thus, it has been found desirable to employ an electrode configuration that includes an additional ground electrode.

[0012]   In yet another embodiment, the invention is directed to a device, comprising:

At least three electrodes, wherein said electrodes are spaced an unequal distance apart and disposed along the fluid flow axis in a flow channel;

means for applying a voltage to the electrodes

to produce a local compositional variation in the fluid;

means for detecting the compositional variation;

means for determining the time-of-flight of the variation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013]   The accompanying drawings, which are incorporated in and form part of the specification, illustrate the present invention and, together with the description, explain the invention. In the drawings, like elements with like functions are referred to by like numbers.

[0014]   Figure 1 shows a schematic embodiment of the invention.

[0015]   Figure 2 shows a second embodiment.

[0016]   Figure 3 is a microfluidic chip including an incorporated time-of-flight flow rate sensor.

[0017]   Figure 4 shows the response of the mass flow sensor to a pulse train.

[0018]   Figure 5 is a plot of the reciprocal of the time-of-flight vs. flow rate.

[0019]   Figure 6 shows a three electrode embodiment of the invention.

[0020]   Figure 7 shows a plot of conductivity vs. flight time for three measurement ranges.

[0021]   Figure 8 shows calibration curves for a three

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electrode system.

DETAILED DESCRIPTION OF THE INVENTION

[0022]   An embodiment of the invention and its operation
are illustrated schematically in FIG. 1. Flow sensor
100 comprises a flow channel **110** having a single fluid
entrance and a single exit where fluid flow is from left
to right. A pair of spaced-apart electrodes **120** for
producing an electrochemical pulse, or pair of pulses,
one on each electrode, and consequent variation in
composition of the fluid, including changes in the
concentration of some component in the fluid, is
disposed within the flow channel and along the flow
axis. Means for supplying a voltage pulse to the
electrodes, such as power supply **130**, is connected to
the electrodes. A flight tube **140** that is concentric
with flow channel **110** can be adjoined to the fluid exit
of the flow channel. As will be appreciated by those
skilled in the art, the dimensions of the flight tube
can be selected for a particular flowrate range and
fluid properties such as viscosity and ionic diffusivity
to govern mass transport and hence, the pressure drop,
response time interval and sensitivity of detection of
the pulse produced by the upstream electrodes. The
flight tube is preferably smaller in diameter than the
flow channel with a length greater than about four times

the diameter in order to achieve rapid transport of the ions to the bulk flow and conveniently short pulse flight times at low flow rates. By way of example, for a flow channel 100 μm in diameter carrying a flow ranging between 10 and 1000 nanoliters/minute, the flight tube is preferably $\approx$5-15 μm in diameter and 0.5 to 2.0 mm long. Detector **150** is designed to detect the pulse in the fluid produced by electrodes **120** and generally comprises a pair of wire electrodes **135**, preferably stainless steel wires or more preferably platinum, palladium, or gold wires, opposite each other and disposed within the flight tube or proximate its exit. Generally, detector **150**, located within flight tube **140**, can be a conductivity sensor that detects changes in conductivity of the fluid caused by changes in the composition of the fluid. Flow rate of the fluid is measured by determining the flight time, the time difference between the creation of the electrochemical pulse and the arrival of the pulse at the detector.

[0023]   The composition variation needed to determine fluid flow rate can be produced in different ways, examples are given below.

[0024]   An electrochemical pulse can be generated by electrolysis of the fluid itself by applying a brief (< 1 sec) electrical current or voltage pulse between

electrodes **120** to produce an electrical charge pulse in
the range of 1-100 microcoulombs. One of the pair of
spaced-apart electrodes acts as an anode and at that
electrode one or more species can be oxidized. The
operation of the flow sensor in this mode can be
exemplified by water as the fluid.

[0025]   Electrolytic oxidation of water under neutral or
acidic conditions produces oxygen gas, a portion of
which remains dissolved in the water, and hydrogen ions.
Consequently, the fluid adjacent the anode becomes more
conductive. At the second of the pair of electrodes,
the cathode, hydrogen ions are reduced to neutral
hydrogen, thereby depleting the region around the
cathode of ions and reducing its conductivity. Under
basic conditions, the opposite is true. Thus, two
pulses or regions of compositional variation are created
at the electrodes and their presence can be detected
downstream by measuring changes in conductivity of the
fluid.

[0026]   An electrochemical pulse useful for measuring fluid
flow rate can also be produced by electrolysis of
dissolved species, such as a redox couple. As before,
local composition variations, i.e., pulses, will be
formed by electrochemical oxidation or reduction of the
redox couple at each electrode, thereby producing a

region of increased or decreased conductivity that can
be used to determine fluid flow rate.

[0027]   Electrodialysis is another method of producing an
electrochemical pulse in a flowing fluid. The advantage
of electrodialysis is that there is no direct
electrolysis of any species in the fluid flow path,
thereby avoiding creating undesirable byproducts in the
fluid such as oxidizing or reducing species that could
interfere with downstream processes. More importantly,
the use of electrodialysis avoids the formation of
electrolytic gas bubbles that could change the fluid
flow regime and interfere with analytical
instrumentation. An embodiment of the invention,
wherein an electrochemical pulse is produced by
electrodialysis is shown in FIG. 2. Here, the pulse
electrodes **120** are separated from the fluid by outer
body **125** that is a material or membrane that provides
for diffusion of water into electrode **120** but not
diffusion out of gas bubbles. The outer body or
membrane can be made from ultra micro-porous, or nano-
porous, glass or an ionomer material. A preferred
material for outer body **125** is Nafion™, a cation-
selective perfluorosulfonate ionomer, that provides for
diffusion of water to electrode **120**.

[0028]   In application, a brief (<1 sec in duration) large

(>1 kV) DC voltage pulse is applied between electrodes
120. Electrolysis at the electrode/Nafion™ interface,
cation transport within the region between body **125** and
electrode **120**, and electrolytic transport within the
fluid result in a region of enhanced ion concentration
at the anode Nafion™/fluid interface and a region of
reduced ion concentration at the cathode Nafion™/fluid
interface. The localized enhancement and depletion
regions (pulses) are advected downstream by the flow to
detector **150**.

[0029]   While the invention has been described and
illustrated by means of a capillary tubes or
microchannels, it is understood that the capillary tubes
and/or microchannels themselves can be part of a
microfluidic device or system. The microfluidic device
or system can be comprised of channels, reservoirs, and
arbitrarily shaped cavities that are fabricated using
any of a number of art recognized microfabrication
methods, including injection molding, hot embossing, wet
or dry etching, or deposition over a sacrificial layer.
The microfluidic device can also include holes and/or
ports and/or connectors to adapt the microfluidic
channels and reservoirs to external fluid handling
devices. The term "microfluidic" refers to a system or
device having channels or chambers that are generally

fabricated on the micron or submicron scale, e.g.,
having at least one cross-sectional dimension in the
range from about 0.1 μm to about 500 μm, i.e.,
microchannels.

[0030]   The time-of-flight fluid flow rate sensor described
above can be fabricated as part of a microfluidic device
such as that shown generally in FIG. 3.

[0031]   Fluid was pumped through flow channel **110** (50 μm
deep, 100 μm wide and about 1 cm long) by pumping means,
such as a syringe pump, and flowed between electrodes
120 located generally at points **A** and **B** along the flow
channel. While the electrodes can be bare wires, it is
preferable in microfluidic applications to use membrane
electrodes, such as the Nafion™-based electrodes
described above, to eliminate the formation of gas
bubbles that can block fluid flow through the narrow
microchannels or form high impedance obstructions to
uniform fluid flow.

[0032]   The Nafion™-based electrodes were fabricated by
injecting a Nafion™ solution (supplied by Dupont as a
5-20% Nafion™ solution in alcohol and water) into a
fritted glass capillary. The Nafion™ solution was
forced through the pores of the frit using gas pressure
and dried to form a 2 mm plug extending a small distance
out from the entrance to the capillary. During drying,

electrical contact was made to the Nafion™ by inserting a wire, preferably stainless and more preferably platinum, palladium, or gold, into the capillary.

[0033]   Fluid flowed from flow channel **110** into flight tube **140** (3 μm deep, 50 μm wide and about 3mm long). Sensor **150**, comprising two opposing electrodes, was positioned at the exit end of the flight tube. After exiting the flight tube, fluid flowed into outlet tube **E**.

[0034]   The ability of the time-of-flight flow sensor to measure fluid flow times reproducibly is illustrated in FIG. 4. A syringe pump was used to pump a solution of water and 0.1 % trifluoroacetic acid (TFA) through the microfluidic device illustrated by FIG. 3 at flow rates ranging from 3.3 nL/min to 830 nL/min. As shown in FIG. 4, two sharp peaks in solution conductivity were observed after a voltage pulse was applied to the Nafion™ electrodes. In order to demonstrate the reproducibility of the method for measuring fluid flow rate, a series of voltage pulses was applied to the electrodes for a fluid flow rate of about 166 nL/min. As can be seen by reference to FIG. 4, the series of conductivity responses were substantially identical.

[0035]   The time-of-flight, i.e., the elapsed time between application of a voltage pulse and detection of the resulting change in conductivity of a fluid, for a

series of fluid flow rates ranging from 3.3 nL/min to 830 nL/min was measured. For purposes of these measurements the time-of-flight was measured from application of the voltage pulse to the centerline of the first conductivity peak. The results of these measurements are shown in FIG. 5 where the logarithm of the reciprocal of the flight time (1/sec) is plotted vs. flow rate. The standard deviation for each data point, except the first, is less than 5% (based on at least 30 measurements).

[0036]   Extensive investigations by the inventors have shown that the sensor configuration disclosed above operates best in the flow rate range of from about 100 nL/min to about 600 nl/min. By way of example, for flow rates of less than 100 nL/min the response time was greater than about 0.2 sec limiting the rate at which flow rate measurements could be taken and thereby making it difficult to use the sensor data for controlling pumps. On the other hand, at higher flow rates ($\approx$1000 nL/min) the short time of flight was a source of noise due to the limited number of data samples that could be taken. While the spacing between the electrode pair could be made smaller, thereby decreasing the response time for the low flow rate condition this solution would only exacerbate the short time of flight experienced for

flow rates in excess of about 600 nL/min. In order to
overcome this problem, it has been found desirable to
employ a three electrode system such as that shown in
FIG. 6.

[0037]   Referring now to FIG. 6. As before, the flow
sensor electrodes are disposed in flow channel **110** that
can be a capillary tube, a microchannel, or a
microfabricated microfluidic chip. The three electrode
flow sensor indicated generally at **600** is comprised of
electrodes **610, 615,** and **620** that together define the
working electrode configuration. Electrodes **625** and **630**
define the conductivity sensing region, designated as **C**
in FIG. 6. In this region electrodes **625** and **630** sense
changes in conductivity of the fluid resulting from
compositional variations produced by electrolysis of the
solvent (e.g., water), electrolysis of a dissolved
species, or electrolysis of a dissolved ionic species,
as discussed above.

[0038]   In order to accommodate the flow rates of interest,
typically from about 10 nL/min to about 10 μL/min, the
electrodes can be spaced a distances that provide for
time of flight measurements of from 20 ms to about 200
ms and data update rates between 10 and 60 Hz. Thus,
for slow range electrodes (flow rates <100 nL/min) a gap
of about 75 microns was provided between pulse injection

and the conductivity sensing region. For medium range
flow rates (flow rates >100 nL/min and <600 nL/min) a
gap of about 500 microns was provided between pulse
injection and the conductivity sensing region. And for
fast flow rates (>600 nl/min) the gap was about 1.4 mm.

[0039]   In operation, a voltage pulse is applied to
adjacent pairs of electrodes. Generally, a voltage
pulse of about -110 V is applied to the electrode
immediately upstream of the grounded electrode for about
1 ms. The short pulse time is selected in order to keep
the concentration of oxygen gas below that required to
form bubbles that could change the fluid flow regime.
As discussed above, membrane electrodes
(electrodialysis) can also be used to eliminate gas
bubbles.

[0040]   In the "fast" mode the voltage pulse is applied to
electrode pair **610** and **615**. For medium range flow
rates, the voltage pulse is applied between electrodes
615 and **620** and, for slow flow rates, between electrodes
620 and **625**. The pulse, formed at the leading edge of
the electrode advects to the conductivity sensing
region. As above, the time elapsed between formation of
the composition pulse and its arrival at the detection
electrodes is used to determine fluid flow rate.

[0041]   It has been found to be preferable to dispose the

electrode system in a channel proportioned to provide conveniently short pulse flight times, preferably less than 1 second, typically having a length to hydraulic diameter ratio greater than 10.

[0042]   The composition pulse is detected as a change in conductivity of the liquid. The conductivity pulse is detected at region C of the flow sensor using a pair of closely-spaced electrodes (625 and 630), preferably platinum electrodes. One of the sensing electrodes is modulated with a small amplitude (<1000 mV) periodic driver signal, such as an AC sine wave, at a frequency of between about 100 Hz to 100kHz with little or no DC bias. An AC current having the modulation frequency is collected from the second of the pair of sensing electrodes and is connected to the input of a low-input impedance circuit. The unprocessed signal is amplitude-modulated relative to the detector driver signal, wherein the fluid conductivity corresponding to the amplitude of the modulating waveform.

[0043]   Electrodes 635 and 640 are added as backflow sensors. Typically, voltage pulse greater than about 110 V is applied between this electrode pair to determine the direction of fluid flow. The voltage pulse is detected at the conductivity sensing electrode pair (625/630). A positive-going pulse indicates

forward fluid flow while a negative-going pulse
indicates reverse flow

[0044]   The three electrode flow sensor described above can
be fabricated by methods known to those skilled in the
art.   Typically:

     Coat a clean a glass wafer with a 0.2 μm silicon
hardmask layer;

     Etch a deep channel pattern into the hardmask using
photoresist and a fluorine-containing silicon plasma;

     Etch deep (50-100 μm) areas of the glass wafer with
HF using the hardmask;

     Overlay the shallow channel pattern onto a new
photoresist layer on the existing hardmask and etch the
pattern into the hardmask;

     Etch both the shallow and deep areas with HF (3-5
μm deep) into the wafer;

     Remove the photoresist and hardmask layers;

     Pattern a new layer of photoresist with the
electrode pattern;

     Etch the glass wafer 0.1-0.2 μm to countersink
electrodes;

     Deposit a metal adhesion layer and an overlaying
electrode layer to fill etched areas through existing
resist pattern;

     Strip off photoresist, lifting off excess metal;

Drill via hole in glass cover plate;

Clean wafer and cover plate surfaces by immersing
in sodium hydroxide solution;

Thermal bond drilled cover plate by high
temperature thermal diffusion;

Attach stainless steel metal wire contacts to the
Pt electrodes by silver epoxy or preferably by
soldering.

[0045]   It has been found that both Ti and Ta adhesion
layers were able to withstand the operating conditions
prevalent in a microfluidic flow sensor device without
peeling. However, an additional constraint on the use
of an adhesion layer is the ability to withstand the
cleaning steps prior to wafer bonding and the high
temperature thermal bonding process itself; conditions
that have been found to damage the Ti adhesion layer.
Consequently, for the flow sensor device Ta is the
preferred adhesion layer material. However, the
combinations of Ta/Pt and Ti/Pt have been found to be
satisfactory sensing electrodes.

[0046]   Referring now to FIG. 7 which shows representative
conductivity traces (magnitude of the conductivity
signal (V) vs. flight time (ms)) for the three
measurement ranges; slow range (10.1 and 77 nL/min),
medium range (630 nL/min) and fast range (1466 nL/min).

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It can be seen that the novel three electrode system described hereinabove was not only capable of measuring flow rates covering two orders of magnitude (>1000 nL/min to 10 nL/min) but also provided a measurable signal at 5 Hz even at flow rates as small as 10 nL/min.

[0047]   It should be noted that in FIG. 7 the pulse was applied at t=0 and the features shown at times less than about 20 ms were artifacts arising from the electronic interactions.

[0048]   A calibration curve for the three electrode embodiment is shown in FIG. 8 as the relationship between flow rate (nL/min) and 1/t(s), where t is the measured time-of-flight for the fast ($\approx$100-1000 nL/min), medium ($\approx$20-500 nL/min) and slow ($\approx$10-100 nL/min) flow rate ranges, for a solution of 5 mM tris methoxyaminomethane (TRIS) at pH 8. Between 100 and 500 measurements were collected at each flow rate to construct the calibration curve. The relationship between flow rate and time-of-flight was found to be linear for each flow rate range with an error in time-of-flight determined to be smaller than the data points shown.

[0049]   The examples above are intended to be illustrative of the application of the present invention and are not to be construed as a limitation or restriction thereon,

the invention being delineated in the claims.

[0050]   In summary, the present invention relates to a
device that can operate at pressures as great as 2,000
psi for measuring fluid flow rates generally, and
particularly in microchannels, over a wide range of flow
rates (<1 nL/min to >10 μL/min). Electrochemical means
are used to produce localized compositional variations
in a flowing fluid at distinct locations along the flow
axis. The compositional variation, or pulse, that is
subsequently detected downstream from its point of
creation is used to derive a flow rate.